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38. (Amended) A method according to claim [36] 37, wherein said detectable label is selected from the group consisting of fluorescent, chemiluminescent and radioactive labels.

REMARKS

Claims 21-82 are pending in the application. The specification has been amended to include continuing application data, and to correct an obvious error in the abstract. Claim 38 has been amended to correct the claim dependency. Claims 21-82, including independent claims 21, 44, and 66, are thus pending for reexamination and reconsideration, which are respectfully requested in view of the foregoing amendments and following remarks.

In the May 27, 1999, Office Action, claims 27-32, 34-37, and 40-82 were rejected under 35 USC §112, first paragraph, for lack of written description. Claims 38 and 39 were rejected under 35 USC §112, second paragraph, as indefinite. Claims 21, 25-30, 34, 37-44, 50-51, 54-60, 66, 72 and 76-82 were rejected under 35 U.S.C. § 103(a) as obvious over Degen in view of Chandler and, "as necessary" Brown III. Claims 23-24, 35-36, 45-46 and 67-68 were rejected under 35 U.S. § 103(a) as obvious over Degen in view of Chandler and Brown III and further in view of Tonucci. The specific grounds for rejection, and applicants response thereto, are set out in detail below.

Rejections under 35 USC §112, First Paragraph

Claims 27-32, 34-37, and 40-82 are rejected under 35 USC § 112, first paragraph, for lack of written description. Specifically, the Examiner states that various terms recited in the claims are not supported in the specification of the application. The Examiner further asserts that it is "not clear" how certain numerical recitations contained in the claims were derived. Applicants respectfully traverse the rejection.

With respect to the recitation of the term "about," the Examiner appears to assert that this term must find support *in ipsis verbis* in the specification for the rejected claim terms. However, the burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not *in ipsis verbis* is insufficient. *In re Edwards, Rice and Soulen*, 568

F.2d 1349, 196 USPQ 465,469 (CCPA 1978). Here, the Examiner fails to provide reasons *why* the term "about" must be recited *in ipsis verbis* support in the specification, and therefore has failed to meet the burden necessary to sustain the rejection under §112, first paragraph.

Moreover, the skilled artisan readily would appreciate that the inventor had possession of the instantly claimed methods, which is the applicable standard for measuring compliance with the written description requirement of §112. In particular, the skilled artisan would recognize that the specification and original claims are replete with recitations of the term "about" as applied to various dimensions and measurements. See, for example, page 8 of the specification, where each and every single dimension is qualified with the term "about." Similarly, every dimension recited in the original claims also is qualified with the term "about." Other dimensions are referred to as "typical," whereas still others are "approximate," Accordingly, the mere fact that the term "about" is not applied specifically to each and every one of the dimensions recited in the specification fails to support an assertion that the inventor did not have possession of the claimed methods that employ various compositions having "about" the recited dimensions. Accordingly, withdrawal of the rejection respectfully is requested.

For claims 37, 55, and 77, the Examiner asserts that it is "not clear" where the specification supports a "generic 'label' other than those recited in claim 9." Applicants respectfully traverse, because the rejection is again based upon an improper requirement for *in ipsis verbis* support for the term "label."

The specification specifically provides examples of radioisotope-, fluorescent-, and chemiluminescent-labeled binding molecules, but nowhere indicates that the claimed methods are limited to the use of such labels. Indeed, methods of labeling biological molecules are widely known in the art, and the skilled worker readily would appreciate that binding molecules to be used in the claimed methods can be labeled using any method known in the art. Moreover, the specification at page 3, line 12, acknowledges that methods of using "labeled" oligonucleotides in hybridization reactions are well-known in the art, further demonstrating that one skilled in the art would recognize that the inventor possessed the claimed methods using "labeled" binding molecules. Accordingly, withdrawal of the rejection respectfully is requested.

For claims 35, 47, and 67, the Examiner asserts that it is "not clear" where the specification supports "glass or silicon" other than "nanoporous glass" or "porous silicon." Applicants respectfully traverse, because the rejection once is again based upon an improper requirement for *in ipsis verbis* support for the term "glass or silicon." In any event, original claim 10 refers to a glass substrate. With respect to "porous silicon" applicants note that the independent claims from which the rejected claims depend recite that the substrate has channels passing from one surface of the substrate to the other surface. A pore is "a minute opening" (MERRIAM WEBSTER'S COLLEGIATE DICTIONARY, 10th Edition). The channels in the substrates are openings in the substrate and, therefore, the silicon must be porous as a result of the channels. Accordingly, one skilled in the art would recognize that the inventor possessed the claimed invention of methods of using silicon substrates, and the rejection should be withdrawn.

The Examiner makes various objections to the format of claim 44, asserting that "it is not clear where the first and second binding reagents for detecting gene expression are supported" and that the claim must recite "gene-specific probes" and "hybridization." The Examiner further alleges that "there is no support for the assay of claim 44 without the limitations of claims 48-49." Applicants respectfully traverse.

Once again, the Examiner appears to be requiring a literal correspondence between various claim recitations and the language of the specification. Section 112, first paragraph, makes no such demand. The Examiner merely states that "there is no support" for certain claim recitations, without explaining *why* this purported lack of support properly may give rise to a rejection under §112. A simple statement that "there is no support," without more, merely restates the rejection and provides no reasoning that explains why one skilled in the art would not recognize that the inventor possessed the claimed method of detecting expression of at least one gene. In the absence of such reasoning, applicants respectfully request that the rejection does not meet the Examiner's burden and request withdrawal of the rejection.

In any event, the Examiner's statements regarding lack of support are unfounded. It is clear from the specification that different groups of channels may contain the same binding reagent. Thus, for example, the specification recites at page 9, lines 21-22 that "substantially homogeneous samples of a pre-determined set of biomolecules, each such

sample being fixed in one or more of said regions" (emphasis added). Similarly, it also is clear that different regions may contain different binding reagents. See page 7, line 27 *et seq.* One skilled in the art would recognize that different binding reagents in different channels amount at least to first and second binding reagents. Accordingly, with respect to the rejection for lack of written description for first and second binding reagents, withdrawal of the rejection is respectfully requested.

The Examiner's assertion that claim 44 must recite "gene-specific probes" and "hybridization" also are unfounded. Presumably, the Examiner's assertion is based upon a supposition that claim 44 somehow is necessarily limited to nucleic acid detection methods. One skilled in the art readily would recognize that gene expression can be measured not only at the nucleic acid level, but also may measured, for example, by detecting the presence and amount of a gene product (a protein) with a reagent such as an antibody. The specification clearly contemplates use of antibodies to detect gene products. See page 10, line 18. Accordingly, withdrawal of the rejection is requested.

With respect to claim 59, the Examiner asserts that Example 11 "disclosed only cDNA" and that therefore there "is no support" for the term "RNA." One skilled in the art is well aware that cDNA is the cognate DNA of an mRNA. Both the cDNA and the mRNA are capable of binding to a complementary nucleic acid strand in the fashion recited in claim 59. In any event, the specification at page 4, line 27, states that "analysis of patterns of gene expression by hybridization of cellular mRNA." Accordingly, claim 59 is literally supported in the specification and the rejection should be withdrawn.

The Examiner next asserts, without further explanation, that the term "polynucleotides" somehow is "overbroad." Without some additional exposition from the Examiner, the exact nature of this rejection is unclear, since the term "polynucleotides," is so well understood in the art that it needs no further explanation. In any event, original claim 2 refers explicitly to "polynucleotides" and the rejection may be withdrawn.

Next, the Examiner posits that "there is no clear support for 'different conditions' in claim 63, since the specification allegedly recites only "different culture conditions." Applicants confess to some puzzlement as to the basis of this rejection. Does the Examiner assert that the skilled worker would recognize that the claimed methods are useful only for comparing gene expression between cells under different culture conditions? Applicants

respectfully submit that one skilled in the art would recognize that the claimed methods are useful for comparing gene expression between any two samples. This is also indicated at page 13, line 29 of the specification that describes a depiction of the use of the claimed methods to "profile gene expression under different experimental conditions." Accordingly, the skilled worker readily would recognize that the applicant had possession of the invention recited claim 63 and the rejection may be withdrawn.

With respect to claim 55, the Examiner asserts that support for claim 64 does not exist in Example 11. Once again it appears that the basis of this rejection is lack of "support "*in ipsis verbis*. However, as explained above, this is not the appropriate standard for measuring compliance with §112, first paragraph. Applicants respectfully submit that the specification clearly refers to comparisons between normal and mutated cells. Moreover, one skilled in the art certainly is aware that gene mutations can and often do affect gene expression in any tissue. Accordingly, the skilled worker would recognize that the applicant clearly possessed the invention of comparing gene expression profiles between normal and mutated cells, and the rejection should be withdrawn.

Next the Examiner rejects claim 55 based upon the assertion that the specification does not support recitations of first and second binding reagents. Applicants response to this argument is discussed *supra* and is repeated here. For the same reasons as set forth above, the rejection is improper and should be withdrawn. The Examiner further posits that "it is not clear how any method "other than 'hybridization' would be supported" or that use of mRNA or cDNA, as recited in claim 81 "would be supported." Applicants respectfully traverse. First, other ways of detecting mutations other than by hybridization are well known in the art. For example, a mutation can destroy the ability of a regulatory element in a gene to bind to a transcription factor. The paragraph at the bottom of page 4 of the specification makes it clear that the claimed methods are useful for studying essentially any detectable biological binding interactions. Furthermore, as described above the specification is replete with references to methods of detecting binding reactions between any polynculeotide, including RNA, mRNA, DNA, and cDNA. Accordingly, the skilled artisan would recognize that the applicant had possession of the claimed invention and the rejection may be withdrawn.

Next, the Examiner posits that "it is not clear where there is support for the method of claim 66 without the limitations of claim 70." This allegedly is so because Figure 5 and Example 10 show different binding reagents in different groups of channels. However, as notedabove, it is clear from the specification that different groups of channels may contain the same binding reagent. See page 9, lines 21-22, stating that "substantially homogeneous samples of a pre-determined set of biomolecules, each such sample being fixed in one or more of said regions" (emphasis added). One skilled in the art would recognize that a mutation can be detected by applying different samples to two different groups of channels containing the same appropriate binding reagent. The presence of binding in one group of channels and of no binding in the other group is indicative of a mutation. Accordingly, one skilled in the art would recognize that the applicant had possession of the claimed invention and the rejection should be withdrawn.

Finally, with respect to the rejections regarding the allegedly "unclear" derivation of certain claim terms, applicants address each rejection in turn:

Claims 29, 50, and 72

The channel cross sectional areas recited in claims 29, 50 and 72 are obtained by applying the formula for the area of a circle (πr^2) to the diameters 33 nm and 10 μm for the channels described, for example, at page 13, line 7 and page 14, line 10, of the specification.

Claims 31, 51, and 73

The channel inner surface areas recited in claims 31, 51, and 73 are obtained by applying the formula for the inner surface area of a cylinder ($2\pi rl$) to channels having diameters 33 nm and 10 μm and lengths (substrate thickness) of 10 μm and 1 mm. These dimensions are recited, for example, at page 13, line 7 (10 μm diameter), page 14, line 10, (33 nm diameter), page 14, lines 28-30 (10 μm thick) and page 14, line 29 (1.0 mm thick).

Claims 32, 52, and 74

The areas of the groups of channels recited in claims 32, 52, and 74 are obtained by calculating the area (πr^2) of groups of channels having a diameter of about 5 μm to about 2000 μm, as described at page 8, line 24.

Claims 34, 54, and 76

The ratios recited in claims 34, 54, and 76 are obtained from the specification at Example 7, last paragraph, which states that "at least 10^7 pBR322 molecules can be attached per mm^2 of glass surface. Based on this density within the pores of the nanofabricated wafer, immobilization of 10^9 -10^{10} molecules of denatured plasmid DNA per mm^2 of wafer cross section are achieved." These data demonstrate that the ratio of inner surface area of a group of channel compared to the surface area of the groups of the channels can be 100 to 1000 (*i.e.* 10^9 -10^{10} divided by 10^7.)

Rejections under 35 USC §103(a)

Claims 21, 25-30, 34, 37-44, 50-51, 54-60, 66, 72 and 76-82 are rejected under 35 U.S.C. § 103(a) as obvious over Degen in view of Chandler and, "as necessary" Brown III. Claims 23-24, 35-36, 45-46 and 67-68 are rejected under 35 U.S. § 103(a) as obvious over Degen in view of Chandler and Brown III and further in view of Tonucci. Applicants respectfully traverse.

Degen in view of Chandler and, "as necessary" Brown III

The Examiner states that Degen discloses porous polyamide membranes that can be used to immobilize acceptor molecules and can be used in immunoassays, and that "the filters of Degen et al. ..... have all of the characteristics of the substrate" recited in claim 1. Chandler is cited as describing immunoassays on a membrane. Brown allegedly teaches that various types of ligands and receptors can participate in binding reactions "like those involved in immunoassays." Applicants traverse on the grounds that, even if the combination of references were proper (which it is not), the combination fails to teach or suggest applicant's claimed invention.

It is axiomatic that, in combining references, the PTO is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make

the combination and (ii) a reasonable expectation that the combination will succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, the Examiner conspicuously has failed to point to any suggestions in cited references that would have motivated one of ordinary skill in the art to combine the references. Accordingly, the rejection is improper and should be withdrawn. Moreover, for the reasons set forth below, the combination of references fails to teach or suggest the claimed invention.

Thus, Degen describes a method for modifying membrane substrates for immobilizing "biologically active material." Degen describes, however, a membrane that is uniformly coated with the "biologically active material" and conspicuously fails to suggest depositing biologically active material in groups of channels in the membrane. Indeed, the membrane design described in Degen would make this task essentially impossible (see Figure 1) and therefore Degen teaches *away* from applicant's claimed invention. Accordingly, Degen neither teaches nor suggests the instantly claimed methods, which use a substrate where the binding reagents are deposited in distinct groups of channels.

This deficiency is not cured by Chandler, which describes methods of carrying out multiple assays on separate filters, *i.e.* individual assays each are carried out on a separate filter. The membrane-bound assays described by Chandler are conventional. See column 2, lines 65-67. Nowhere does Chandler teach or suggest methods of carrying out binding assays in channels or groups of channels on the same substrate, nor does Chandler suggest immobilization of binding reagents on the walls of channels in the substrate. Moreover, Chandler fails to teach or suggest methods using two or more different reagents in two or more groups of channels. Brown also cannot cure the deficiencies of Chandler and Degen, merely stating that various types of ligands and receptors can participate in binding reactions "like those involved in immunoassays."

In sum, for the reasons set forth above, the cited references may not properly be combined. Moreover, even if combined, the references fail to teach or suggest the

instantly claimed invention. Accordingly, the rejection is improper and should be withdrawn.

Degen in view of Chandler and Brown III further in view of Tonucci

The Examiner states that Tonucci teaches use of nanochannel glass filters, that the membranes of Degen are "functional" equivalents of Tonucci's filters, and that it would have been obvious to use the Tonucci filters in the assays taught be Degen. Applicants respectfully traverse.

The deficiencies of Degen, Chandler, and Brown III are described in detail *supra*. Tonucci, which merely describes nanochannel glass and its use as a filter cannot cure these deficiencies. In filtration methods, the material to be filtered is applied uniformly to the filter to achieve optimal filtration. Thus, by describing use of nanochannel glass as a filter material for separations and thereby suggesting the uniform application of a material to the filter Tonucci, like Degen, teaches away from the claimed invention, where binding reagents are deposited in distinct groups of channels on the substrate. Accordingly, the cited references fail to teach or suggest the instantly claimed invention, and the rejection is improper and should be withdrawn.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional extension(s) of time are required for the filing of this paper, applicants expressly petition for such extension(s) and authorize the Commissioner to charge any deficiency to Deposit Account 19-0741.

Respectfully submitted,

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Date

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